REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 18-22, 24-39 and 65 are currently pending. Claims 18 and 24 have been amended for clarification purposes and to advance one aspect of the invention. Support for the amendments can be found throughout the specification and at specific sections as noted in the following remarks. The amendments are made without prejudice to filing a continuation, continuation-in-part, or divisional thereon. No new matter has been added.

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 18-22, 24-39 and 65 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Action maintains the specification is enabling for making and using single-chain antibody-streptavidin fusion proteins. In particular, the Action states the specification is enabled for the single-chain antibody-streptavidin fusion proteins huNR-LU-10 scFvSA and B9E9 scFvSA. However, the Action maintains that, while the methodology necessary to determine whether a particular species of the claimed genus of streptavidin fusion proteins might be known in the art, the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to have a reasonable expectation of successfully making and using at least a substantial number of the members of the claimed genus comprising variants without undue experimentation. Additionally, the Action maintains that due to the complexities of engineering antibodies, the skilled artisan could allegedly not have a reasonable expectation of success in making and using at least a substantial number of members of the claimed genus of fusion proteins comprising an antibody or antigen-binding fragment thereof without undue experimentation.

Applicants traverse this ground for rejection in view of the following remarks. Applicants disagree with the Action's assertion that it would require undue experimentation to make and use fusion proteins comprising variants of SEQ ID NO:2. In particular, Applicants

submit that the skilled artisan would readily appreciate that generating species within the 90% genus requires only routine experimentation using procedures known in the art, such as any number of mutagenesis schemes used routinely in the art. Furthermore, illustrative procedures are described in the instant specification for example, at page 8, line 16 - page 9, line 24 and page 11, lines 2-10.

Applicants further submit that the mere presence of some inoperative embodiments within the scope of a claim does not render a claim nonenabled. The standard is whether one of skill in the art could determine which embodiments would be inoperative without undue experimentation (see MPEP § 2164.08(b)). Applicants submit that the skilled artisan would readily appreciate in light of the instant specification not only how to generate genomic streptavidin fusion proteins having 90% identity to the native sequence thereof, but also how to determine whether such a genomic streptavidin fusion protein could bind biotin. In particular, see for example, page 8, line 16 - page 9, line 24 and page 11, lines 2-10 of the specification as filed. Furthermore, the skilled artisan would readily recognize the routine nature of determining the operative or inoperative species of streptavidin fusion proteins, particularly given the teachings in the instant specification. In particular, the assays for measuring biotin binding, described in the specification at page 11, lines 2-10 are well known to the skilled artisan and are used routinely in the art.

Notwithstanding the above and without prejudice, Applicants have amended the claims to remove recitation of variants. Therefore, Applicants submit that this basis for rejection has been obviated and the rejection may be properly withdrawn.

With regard to the assertion that due to the complexities of engineering antibodies, the skilled artisan could allegedly not have a reasonable expectation of success in making and using at least a substantial number of members of the claimed genus of fusion proteins without undue experimentation, Applicants assert that while engineering antibodies may be a complex process, it is a process that is well known in the art, is well within the skill of the ordinarily skilled artisan, and is described in the instant specification. The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required.

The burden is on the PTO to establish that experimentation would be undue, *Angstadt*, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether disclosure requires undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may be required to practice the present invention does not rise to the level of being *undue* experimentation, as defined by the Court in *Wands*.

An important aspect of the Court's decision in *Wands* is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a *broad* definition of the term "experiment". The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a particular antigen. As described by the Court, the process entailed, "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening for antibodies produced by the hybridomas for the desired characteristics." 8 U.S.P.Q. 2d at 1407. Thus, *Wands* supports the conclusion that in a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes *one* experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma making the desired antibody. 8 U.S.P.Q.2d at 1406. Thus, the fact that some aspects of the experiment as a whole will yield negative results does not mandate finding that the amount of experimentation to achieve a positive result is undue.

Thus, the production of the claimed fusion proteins comprising an antibody or antigen-binding fragment thereof may require some experimentation, but if viewed in the light of *Wands*, this experimentation, and the possibility of encountering negative results along the path to the positive results, is not undue. Furthermore, the instant specification provides extensive guidance, including two working examples (*e.g.*, the single-chain antibody-streptavidin fusion proteins huNR-LU-10 scFvSA and B9E9 scFvSA) to allow one of ordinary skill in the art to generate both antibodies and genomic streptavidin fusion proteins comprising said antibodies.

In view of the above remarks, Applicants urge that the pending claims are more than adequately enabled by the instant specification. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §103(a), Obviousness

Claims 18-39 and 65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dubel, *et al.* (J. Imm. Meth. 178: 201-209, 1995), as evidenced by Kipriyanov, *et al.* (Hum. Antibod. Hybrid. 6: 93-101, 1995), in view of Desplancq, *et al.* (Prot. Eng. 7: 1027-1033, 1994), Anderson, *et al.* (Clin. Immnol. Immunopath. 84: 73-84, 1997), McLaughlin, *et al.* (Onc. 12: 1763-1769, 1998), the internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia), Gallizia *et al.* (Prot. Exp. Pur. 14: 192-196, 1998), and Pahler, *et al.* (J. Biol. Chem. 262: 13933-13937, 1987), Aragarana, *et al.* (Nuc. Acids Res. 14: 1871-1882, 1986), Ohno *et al.* (DNA and Cell Biol. 15: 401-406, 1996), and Goshorn, *et al.* (Canc. Res. 53: 2123-2127, 1993).

As discussed in previous responses, Applicants submit streptavidin fusion proteins of the invention, comprising at least 129 amino acids of streptavidin, are non-obvious in light of the prior art's use of fusion proteins comprising core streptavidin, amino acids 14-136. Applicants reiterate in particular that the Aragarana *et al.* and Pahler *et al.* references disclose that the N-terminal and C-terminal amino acids of streptavidin can be discarded without streptavidin loss of ability to bind biotin. Furthermore, Pahler *et al.* state in the abstract that "Core streptavidin is more soluble than is the parent molecule." Therefore, these references in fact teach away from the instant invention.

Applicants further submit that genomic streptavidin fusion proteins provide substantial and heretofore unrecognized advantages over core streptavidin fusion proteins, including protein folding and secretion into the periplasmic space. Such advantages circumvent the need to extract the protein from the cytoplasm, as necessary for core-streptavidin fusion proteins. Applicants submit the use of genomic streptavidin in fusion proteins remedies a shortcoming of using core-streptavidin in fusion proteins and was surprising in light of the prior

art, which consistently used core-streptavidin. As the courts have found, the presence of a property not possessed by the prior art is evidence of nonobviousness. (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Therefore, the cited references not only do not teach or suggest the presently claimed genomic streptavidin, Applicants further submit that none of the cited references teach or suggest that the introduction of additional amino acid residues to the amino- or carboxy-terminal end of core streptavidin would provide the advantages demonstrated in the instant application, e.g. secretion into the periplasmic space and production of soluble, easily purified streptavidin fusion protein. Such unexpected findings clearly render the presently claimed invention non-obvious in light of Dubel, *et al.*, or any of the cited prior art references. This is further supported by the enclosed Declaration of Dr. Stephen C. Goshorn.

Applicants submit that the claims are nonobvious under 35 U.S.C. § 103(a) and respectfully request this basis of rejection be withdrawn.

Rejection under 35 U.S.C. §112, Second Paragraph, Indefiniteness

Claim 34 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. In particular, the Action contends that, because claim 34 contains the trademark Primatized™, it does not comply with the requirements under 35 U.S.C. § 112, second paragraph.

Applicants respectfully submit that claim 34 was amended to remove recitation of Primatized™ in Applicants response to the Office Action mailed June 22, 2001, filed on November 30, 2001. As shown in the listing of claims on page 4 of this response, claim 34 currently reads: The fusion protein of claim 33, wherein the antibody or fragment thereof is a humanized antibody. Applicants respectfully submit that claim 34 complies with the requirements under 35 U.S.C. § 112, second paragraph and urge that the rejection may be properly withdrawn.

Double Patenting

Claims 18-22, 26, 28, and 33-39 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-26 and 71-80 of co-pending Application No. 10/150,762.

Claims 18-22, 24-39, and 65 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-42 and 77-81 and 71-80 of co-pending Application No. 10/013,173.

Applicants respectfully request that the above rejections be held in abeyance until allowable subject matter is identified herein and the above co-pending applications have been examined.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Stephen C. Goshorn et al.

SEED Intellectual Property Law Group PLLC

William T. Christiansen, Ph.D.
Registration No. 44,614

WTC:jto

Enclosure:
Postcard
Declaration of Dr. Stephen C. Goshorn

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

C:\NrPortbl\iManage\JOHNO\353909_1.DOC